European Federation of
Pharmaceutical Industries
and Associations

Fédération Européenne
d'Associations et d'Industries
Pharmaceutiques

Ref: CLJ. IC/60.201 **1 December 2004**

Dockets management branch (HFA-305)
FOOD AND DRUG ADMINISTRATION
5630 Fishers Lane, rm 1061
Rockville,
USA - MD 20852

Dear Sir/Madam,

Re: EFPIA Comments on FDA Guidance for Industry: quality Systems Approach to Pharmaceutical current Good Manufacturing Practice Regulations
(Docket Number: 2004D-0443)

Please find enclosed EFPIA comments with respect to the above-mentioned document.

We thank the FDA for providing us with the opportunity to comment on this document and remain,

Yours sincerely,

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Head of Scientific, Technical & Regulatory Affairs

Cc: E. Cooke (EMEA)
J-L Robert (Laboratoire national de Santé, Luxembourg)

Encl. EFPIA comments

2004D-0443 C15

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General comments

EFPIA wishes to congratulate the FDA in maintaining momentum with its Science and Risk based initiatives for Pharmaceutical Development and Manufacturing, including the issue of this guidance which represents an important milestone and update in the thinking of the FDA and its philosophy towards pharmaceutical development and manufacturing. It is welcomed that FDA recognises that cGMP regulations do not consider all of the elements that today constitute most quality management systems.

EFPIA is fully supportive of the intent of this document. EFPIA is very supportive of the need to modernise and to harmonize pharmaceutical Quality Systems and regulatory processes to enable a culture of Quality improvement, whilst building in some potential for regulatory flexibility for the filing of changes and inspectional coverage for companies showing good product and process knowledge and good quality systems.

We believe this guidance provides industry a significant additional impetus to change its manufacturing and quality process philosophy from a reactive post-manufacturing quality testing regimen into one directed towards a manufacturing operation focussing on proactive control and based on science and technology, with quality designed into the process and the product in order to achieve business process excellence.

We would urge the FDA to include within the scope of the quality systems some additional aspects such as:

- Information Management Systems. Information management is the key to most of our business processes and the need to manage data, knowledge and experience gathered has become an essential element. The requirements for computer system validation do not encompass the concept of managing business processes and managing information.
- Corporate Quality Systems. For globally operating companies, the global and local quality systems need to be harmonised. This aspect is often mentioned during FDA inspections and it would be useful to make a reference to the scope of corporate and local quality systems.

Specific comments

Inspection Scope (reference line 290, 304 – 335, 390 - 393)
It is welcomed that this document gives guidance on how the implementation of comprehensive quality systems can help manufacturers achieve compliance, but does NOT create new expectations for pharmaceutical manufacturers that go beyond the requirements laid down in current regulations. Although industry welcomes a quality systems approach to inspections, some of the guidance given in this document, for example:

- the expectations for management, (lines 304 – 334)
- the requirement to use "a formal quality planning process" and "measurable goals that are monitored regularly " (line 390 – 393)

although sound and valid, go beyond the current regulations. Care needs to be taken that this guidance does not raise the expectations of inspectors or lead to the citation of deviations related to this guidance as opposed to deviations related to compliance with the cGMP regulations. There are also several examples of cGMP requirements being compounded in sentences with non-cGMP requirements. Some examples are lines 518-521, lines 674-683, lines 543 – 547. Clear communications are needed to position this guidance with the status of the cGMP regulations. It is stated (line 290) that FDA will only inspect against CFR requirements. This is necessary. However, it would be desirable to clarify that inspections should be conducted using the document entitled 'Risk based method for prioritizing cGMP inspections of pharmaceutical manufacturing sites', published by the FDA in September 2004. This will not only facilitate the inspection but will also be the start of a consistent global approach, moving the industry and the regulators from a compliance mentally to a science and risk based quality systems model. EFPIA recommends that references to cGMP regulations be deleted and that it is clearly stated that the paper is only intended to be guidance for a model quality system. This will facilitate the use of the guide for both drug products and drug substances and will also facilitate its use as a model for an internationally harmonized quality system guide.

Implementation of Regulatory Flexibility (reference lines 98 – 103)
The principles outlined in lines 98-103 are fully supported. Further clarity will need to be developed on the mechanisms as to how Industry and FDA will work together to define and apply 'regulatory flexibility' for filings and inspections where a company meets the criteria for good process knowledge and good quality systems.

Scope of the document (reference line 116)
The scope of the document should also include specific reference to Drug Substance (API) manufacture, as it is not clear if this is included. Many companies operate one quality system for all their manufacturing sites, whether they are for drug substance or drug product manufacture and the Quality System approach is equally applicable to drug substance and drug product manufacturers.

If APIs are included in the scope, components should not be mentioned,(line 116) as this raises expectations beyond current requirements.

References to GMP
The specific references to selected parts of the cGMPs seen in a number of areas in the document should be removed from the guidance to avoid potential confusion. In addition, as this document should be equally applicable to APIs as to drug products, if the cGMP references are kept, they should also include the references to the GMP

guidance for APIs (Q7A). An alternative mechanism rather than this guidance could be Q&As on the FDA website, which could be used to address specific cGMP interpretations (e.g. lines 613-619 on alternative approaches to assuring the reliability of suppliers).

Definition of Achieving Quality (reference Line 154)
Achieving Quality is defined in the document as "achieving identity, strength, purity, and other quality characteristics designed to assure the required levels of safety and effectiveness". This is a narrow definition which could be further improved to be more in line with the tone of the guidance. There is such synergy between the concepts of process understanding, manufacturing science, and quality by design that to limit quality in this manner is to equate quality with meeting specifications. This is part of moving from a compliance mentality to a quality systems approach including science driven basis for determining quality. A better definition of quality and achieving quality would incorporate these concepts.

Innovation, Process Improvement and Optimisation (reference lines 175-183 and 195)
In section III. "CGMPS and the concepts of modern quality systems", it is felt that the element of process improvement and optimisation is missing.. Section D Lines 175 to 183 deals with CAPA, but as pointed out in the white paper on Innovation and Continuous Improvement, a modern quality system needs to look at improvement and optimisation before problems arise. The concept of improvement and optimisation therefore needs to be addressed. In addition the concept of innovation needs to be addressed, particularly as the need for innovation is a driving force behind the FDA's initiative.

Distinction between QA and QC (reference lines 207 -212)
The distinction which is now made between QC and QA is welcomed. This distinction brings cGMP into line with GMP requirements in other regions and also recognises that this is the way in which most pharmaceutical companies are organised.

Broadening the Concept from Change Control to Change Management (Reference lines 185 and 708)
It is recommended that the term Change Management is used instead of Change Control. Change Management is more encompassing than change control and is more consistent with the quality management approach. Change Control is still reminiscent of a quality control unit which reviews and dispositions change requests. Change Management is considered to be more comprehensive including not only changes to procedures but changes to equipment, specifications, etc. Change Management is more conducive to enabling change to be made in a risk based manner taking into account the integral nature of pharmaceutical systems. Change Management also conveys the concept that change is desirable albeit in a managed process as opposed to change is something that is bad and must be controlled.

Invalidation of Test Results (reference line 730)
The word "statistically" should be deleted from the statement "invalidation of test results should be scientifically and statistically sound and justified".
FDA has previously not required statistics be used to invalidate a test result. This requirement is therefore inconsistent with other draft guidances and should not be included in this guidance.

Auditing (reference line 808)
On line 808 there is a requirement to audit the entire system at least annually. It is felt that a risk based approach to audits should be taken, with those areas and systems having a higher risk being audited more frequently and low risk areas being audited less frequently. These are the same principles to those outlined in the FDA's new policy for risk-based inspections.

References to ongoing activities
We suggest that references to other 'ongoing' activities (e.g. footnotes 4,5,6.) are removed, or added as true references.